# EXHIBIT A-1

**UNITED STATES DISTRICT COURT**
**FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA**
**CHARLESTON DIVISION**

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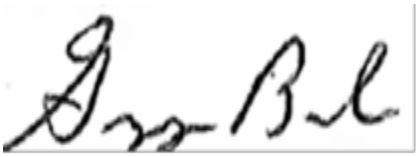
| **IN RE: ETHICON, INC.**<br>**PELVIC REPAIR SYSTEM**<br>**PRODUCTS LIABILITY LITIGATION** | **Master File No. 2:12-MD-02327**<br>**MDL No. 2327**<br><br>**JOSEPH R. GOODWIN**<br>**U.S. DISTRICT JUDGE** |

# DEFENSE EXPERT GENERAL REPORTS

# OF GREGORY BALES, M.D.:

Prepared by



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Gregory Bales, M.D.

March 2, 2016

I make this report in connection with the cases involved in the Ethicon, Inc., et al. litigation and hold all opinions stated herein to a reasonable degree of medical certainty.

## I. PELVIC ORGAN PROLAPSE

Pelvic organ prolapse (POP) occurs when female pelvic organs such as the bladder, uterus, or rectum, descend into the vagina. This is typically caused by failure of the supporting structures in the pelvis. Risk factors include age, vaginal child birth, chronic heavy lifting or straining, smoking, obesity, loss of muscle tone, estrogen loss associated with menopause, family history, pelvic trauma or previous surgery, chronic constipation, chronic cough, and connective tissue disorders.

The exact prevalence of POP is difficult to ascertain due to the number of women with POP who do not seek medical attention. Current estimates are that 6 to 8 percent of women report symptoms of POP

The severity of a woman's POP is measured using the POP-Q or other classification system. This system categorizes pelvic organ prolapse on a scale of 0 to 4 based on the lowest extent of protrusion in the standing and straining position.

### A. TREATMENT OPTIONS

POP can be treated conservatively (non-surgically) or surgically. Conservative treatments include pelvic floor muscle training or the use of a pessary. The use of a pessary has very low risk but is not typically an acceptable treatment option for women who are sexually active.

Surgical treatment of POP is offered as a more permanent treatment option for patients who are bothered by their POP symptoms. One surgical option, most often used as a treatment for uterine or vaginal vault prolapse, is the abdominal sacrocolopexy (ASC), the open attachment of the vaginal apex to the anterior longitudinal ligament of the sacrum just inferior to the sacral promontory. After a comprehensive review in 2004, Success rates averaged about 80% - 95% in the short to medium term of 6 months to 3 years. However, success rates dropped to 50% after just seven years. Complications specific to ASC may include injuries to the femoral, obturator, peroneal and/or sacral nerves, sacral osteomyelitis, and/or gluteal necrotizing myofascitis. If mesh is used, it can erode or become exposed. Although ASC offers good short and medium term success rates, the risks and morbidity associated with the technique are high. It is not surprising that alternative approaches were developed to minimize the invasiveness of the ASC.

Two additional apical support techniques utilizing a completely transvaginal approach are the uterosacral vaginal vault suspensions (ULS) and the sacrospinous ligament fixations (SSLF). As transvaginal operations, these approaches eliminated the transabdominal dissection required of the ASC with lower risk of bowel or bladder injury, major hemorrhage or post-operative ileus or bowel obstruction.

Nevertheless, even these transvagainal approaches were not without unique risks. The ULS was known to cause ureteral occlusion in up to 11% of patients with 4% requiring reimplantation in one study. In a review of the SSLF, the major complaint was buttock pain that occurred in 3% of subjects, although a vast majority resolved by 6 weeks postoperatively. Only

severe pain radiating down the leg represented sciatic nerve entrapment requiring suture removal. Unfortunately, the ULS and SSLF both had a success rate of only 60% at 2 years. [1] Dyspareunia is a known risk as well and de novo dyspareunia rates of 26% have been reported for ULS and 36% for SSLF.[2]

Colporrhaphy is a surgical technique to treat anterior and posterior prolapse. High rates of recurrence of 30% or more have been reported with colporrhaphy particularly in the anterior compartment.[3] It comes with associated risks of pain, dyspareunia, injuries to adjacent nerves and structures and other problems.

Due to the shortcomings associated with these "native tissue" surgical procedures, surgeons began using mesh for the treatment of POP. It started with the use of mesh in ASC. After that, in the 1990s, pelvic surgeons began to use mesh transvaginally, in order to take advantage of the fewer complications which result from the use of that approach. Because no meshes specific for this surgery were on the market, surgeons would trim a piece of sheet of mesh and fashion it to lie on the repair. At the time, surgeons used the same mesh as that used in abdominal surgery.

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[1] Barber MD, et al. Comparison of two transvaginal surgical approaches and perioperative behavioral therapy for apical vaginal prolapse: the OPTIMAL randomized trial. JAMA. 2014;311(10):1023

[2] Lowman JK, et al. Does the Prolift system cause dyspareunia? Am J Obstet Gynecol. 2008;199(6):707.e1-6; Silva WA, et al. Uterosacral ligament vault suspension, five-year outcomes. Obstet Gynecol 2006;108:255-63; Maher CF, et al. Abdominal sacral colpopexy or vaginal sacrospinous colpopexy for vaginal vault prolapse: a prospective randomized study. Am J Obstet Gynecol 2004; 190:20-6.

[3] Weber AM, et al. Anterior colporrhaphy: a randomized trial of three surgical techniques. Am J Obstet Gynecol 2001;185:1299-304; Sand PK, et al. Prospective randomized trial of polyglactin 910 mesh to prevent recurrence of cystoceles and rectoceles. Am J Obstet Gynccol 2001;184:1357-62; Whiteside JL, et al. Risk factors for prolapse recurrence after vaginal repair. Am J Obstet Gynecol. 2004 Nov;191(5):1533-8.

In January of 2002, GYNEMESH PROLENE® Soft polypropylene mesh was cleared for pelvic floor repair. The labeling for Gynemesh PS did not suggest or specify whether the surgeon would use the product with a trans-abdominal or trans-vaginal approach. Gynemesh is considered light weight and macro-porous. Surgeons cut Gynemesh into the shapes they preferred for POP repair, or used it with anterior colporrhophy. Using Gynemesh transvaginally was a safe and effective approach to the treatment of POP, and remains a safe and effective product for use with ASC. The next step in the evolution of pelvic floor repair was to create a standardized, reproducible and reliable technique for the treatment of pelvic organ prolapse.

With this goal in mind, Ethicon introduced the Gynecare Prolift pelvic floor repair system in March of 2005. Using an ergonomically designed guide, cannula and retrieval device, the Gynecare Prolift pelvic floor repair system delivered precut Gynecare Gynemesh PS polypropylene mesh to essentially recreate the normal anatomic pelvic floor.

Since its inception, the Gynecare Prolift pelvic floor repair system has been involved in over 100 studies. In comparison, the traditional repairs, including the ASC, ULS and SSLF were performed and modified for decades before ever being investigated in a single randomized control trial.

The success of vaginal mesh techniques, especially in the anterior compartment, has been proven in several randomly controlled trials. In a recent comprehensive review, the

differences in success rates of vaginal mesh techniques compared to native vaginal tissue repairs were significant.[4]

**Table 1** Randomised controlled trials comparing polypropylene mesh with traditional native vaginal tissue repairs

| Reference | Total number patients | Follow up (months) | Compartment studied | Anatomic cure mesh (%) | Anatomic cure traditional (%) | *p* |
|---|---|---|---|---|---|---|
| Hiltunen et al. [9] | 104 | 12 | Anterior | 93 | 62 | <0.04 |
| Sivaslioglu et al. [10] | 90 | 12 | Anterior | 91 | 72 | <0.05 |
| Nieminen et al. [11] | 105 | 24 | Anterior | 89 | 59 | <0.05 |
| Nguyen and Burchette [12] | 75 | 12 | Anterior | 87 | 55 | <0.05 |
| Carey et al. [13] | 139 | 12 | Anterior Posterior | 81 | 65.6 | 0.07 |
| Nieminen et al. [14] | 202 | 36 | Anterior | 87 | 59 | <0.0001 |
| Withagen et al. [15] | 194 | 12 | All | 90 | 55 | <0.001 |
| Altman et al. [16] | 389 | 12 | Anterior | 82 | 48 | 0.008 |
| Sokol et al. [17] | 65 | 12 | All | 38 | 30 | 0.45 |

After years of study, the conceptual advances in the surgical management of genital prolapse that resulted in the Gynecare Prolift pelvic floor repair system were beginning to achieve the success rates previously achieved only by the more invasive abdominal approaches such as the ASC. More recent Prolift studies continue to show significantly better cure rates compared to native vaginal tissue repairs as well as high levels of subjective improvements, patient satisfaction and quality of life.[5] The largest study, by Altman, also showed statistically significant improvements in subjective cure assessed as sensation of bulging compared to native tissue and another recent large study showed significantly better cure, as well as prolapse quality of life scores, when compared to native tissue.[6]

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[4] Jacquetin B, et al. Total transvaginal mesh (TVM) technique for treatment of pelvic organ prolapse: a 5-year prospective follow-up study. Int Urogynecol J. 2013;24(10):1679

[5] Halaska M, et al. A multicenter, randomized, prospective, controlled study comparing sacrospinous fixation and transvaginal mesh in the treatment of posthysterectomy vaginal vault prolapse. Am J Obstet Gynecol. 2012;207(4):301.e1-7; Svabik K, et al. Comparison of vaginal mesh repair with sacrospinous vaginal colpopexy in the management of vaginal vault prolapse after hysterectomy in patients with levator ani avulsion: a randomized controlled trial. Ultrasound Obstet Gynecol. 2014 Apr;43(4):365-71

[6] Dos Reis Brandão da Silveira S, et al. Multicenter, randomized trial comparing native vaginal tissue repair and synthetic mesh repair for genital prolapse surgical treatment. Int Urogynecol J. 2015;26(3):335-42.

B. COMPLICATIONS

When compared to the other procedures used to treat POP, the intra-operative complications associated with the Gynecare Prolift and Gynemesh PS were comparable. Intraoperative rates of bladder perforation (3%), rectal perforation (1%), major hemorrhage (1%), and vaginal hematoma (2%) were all low.[7] Perioperative complications such as urinary retention (2%), anemia (1%), wound infection (1%), groin pain (2%), buttock pain (0%), fever (2%) and blood transfusions (1%) were also acceptably low. [8] Dyspareunia rates were very acceptable and approximately the same as native tissue surgeries in most studies. (can cite Lowman here-put in the citation)

The only unique risk with Prolift or Gynemesh PS is mesh exposure and erosion, which was well known to surgeons.[9] Moreover, mesh exposure and erosion had long been discussed in the medical literature. The exposure and erosion complications were outlined in various materials such as the Prolift instructions for use, surgical technique guide, professional education, and the Prolift Surgeon's Resource Monograph.

There are several patient-driven factors that increase the risk of wound complications following prolapse surgery, including mesh exposure. [10] Smoking, poorly controlled diabetes,

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[7] Altman D., et al. Short-term outcome after transvaginal mesh repair of pelvic organ prolapse. Int Urogynecol J. 2008;19(6):787

[8] Altman D, et al. Perioperative morbidity using transvaginal mesh in pelvic organ prolapse repair. Obstet Gynecol. 2007;109(2):303

[9] Abed H, et al. (2011). Incidence and management of graft erosion, wound granulation, and dyspareunia following vaginal prolapse repair with graft materials: a systematic review. Int. Urogynecol J (2011) 22:789-798.

[10] Deng T, et al. Risk factors for mesh erosion after female pelvic floor reconstructive surgery: a systematic review and meta-analysis. BJU Int. 2015; (Epub ahead of print)

early return to exercise, lifting or vaginal sexual activity, and non-compliance with estrogen supplementation has been noted as risk factors and these are generally under the control of the patient. Younger age, higher parity and concomitant hysterectomy are also factors, although the patient cannot modify them.

In addition to exposure and erosion, Plaintiffs' experts' opine that dyspareunia and contraction are unacceptably common with Prolift. Each is addressed in turn below.

1. *Dyspareunia*

Dyspareunia is a long-standing, well-known complication that is well established in the surgical literature regarding the surgical repair of POP. Just as scars may result from incisions, all surgeons (not only pelvic surgeons) should reasonably understand that sexual dysfunction and pain may occur with vaginal surgery and convey that information to their patients preoperatively. Overall, the studies comparing Prolift to native tissue repairs do not show any statistically significant differences in rates of de novo dyspareunia, pelvic pain or sexual dysfunction.[11]

2. *Contraction*

There is no medical literature conclusively establishing that mesh contracts with vaginal use to clinically significant degrees.[12] It is well-known that there will be scar formation in

[11] Maher C, Feiner B, Baesler K, Schmid C. Surgical management of pelvic organ prolapse in women (Review). Cochrane Database of Systematic Reviews 2013, Issue 4. Art. No.: CD004014. DOI:10.1002/14651858.CD004014.pub5; Maher C, Feiner B, Baessler K, Christmann-Schmid C, Haya N, Marjoribanks J. Transvaginal mesh or grafts compared with native tissue repair for vaginal prolapse. Cochrane Database of Systematic Reviews 2016, Issue 2. Art. No.: CD012079. DOI:10.1002/14651858.CD012079.

[12] Dietz HP, et al. Mesh contraction: myth or reality? Am J Obstet Gynecol. 2001;204(2):173

association with a foreign body such as mesh and that scar tissue can contract. The Gynecare Prolift is intended to be placed in complete contact with the tissue, without folding or bunching. If an appropriate tension free setting of the mesh was accomplished during surgery, even if mesh contraction were to occur, it would unlikely be clinically noticeable. If the mesh was placed under tension, folded, bunched or otherwise sub-optimally placed, then mesh contraction could conceivably cause erosion, dyspareunia or pelvic pain. This potential complication is well known to properly trained surgeons.

3. *Other Complications*

There have also been claims that the mesh degrades, is cytotoxic, leads to an adverse significant inflammatory response, and that it causes sarcoma formation or cancer. However, the clinical data is inconsistent with this theory as there are long-term studies of efficacy and safety. Additionally, the macroporous Prolene material has been studied in the body for up to 17 years showing its long-term biocompatibility. The data do not show a malignant risk.[13]

[13] AUGS-SUFU FAQs by Providers on Mid-urethral Slings for SUI 2014; AUGS-SUFU Position Statement on Mesh Midurethral Slings for SUI 2014; Nilsson CG, et al. Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J. 2013;24(8):1265-9; Svenningsen R, et al. Long-term follow-up of the retropubic tension-free vaginal tape procedure. Int Urogynecol J. 2013;24(8):1271-8; Serati M, et al. Tension-free vaginal tape for the treatment of urodynamic stress incontinence: efficacy and adverse effects at 10-year follow-up. Eur Urol. 2012;61(5):939-46; Elmer C, et al. Histological inflammatory response to transvaginal polypropylene mesh for pelvic reconstructive surgery. J Urol. 2009;181(3):1189-95; Smith TM, et al. Pathologic evaluation of explanted vaginal mesh: interdisciplinary experience from a referral center. Female Pelvic Med Reconstr Surg. 2013;19(4):238-41. Falconer C, et al. Influence of different sling materials on connective tissue metabolism in stress urinary incontinent women. Int Urogynecol J Pelvic Floor Dysfunct. 2001;12 Suppl 2:S19-23; King AB, Goldman HB. Current controversies regarding oncologic risk associated with polypropylene midurethral slings. Curr Urol Rep. 2014;15(11):453; King AB, et al. Is there an association between polypropylene midurethral slings and malignancy? Urology. 2014;84(4):789-92;Moalli P, Brown B, Reitman MT, Nager CW. Polypropylene mesh: evidence for lack of carcinogenicity. Int Urogynecol J. 2014;25(5):573-6.

Plaintiffs' experts also claim that there were safer alternative meshes to the Prolift. The theory that an even larger pore and lighter weight mesh would be better has not withstood clinical scrutiny. One such mesh, Vypro, was studied by the TVM Group and found to not be tolerable.[14] Other meshes do not have a higher efficacy profile nor have the data shown them to be safer overall. There is still a risk of mesh exposure with the use of any mesh.

In summary, Prolift has been demonstrated to be safe and effective. Longer term studies continue to show its efficacy and safety.[15]

C. PROLIFT IFU

Instructions for use (IFU) accompany all medical devices like the Prolift. I will testify that the Prolift IFU adequately warned of all risks and potential complications associated with the Prolift. I will also testify that these risks were well known to the medical community.

It is important to note that an IFU is not intended to serve as a comprehensive guide for a surgeon. Instead, it provides information about the device, the procedure, the indications, and warnings and precautions that the surgeon can use in conjunction with his or her training and experience. A reasonably prudent surgeon will be trained in pelvic floor surgery, with or without mesh, before he or she attempts to implant a Prolift.

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[14] Denis S et al. Pelvic organ prolapse treatment by the vaginal route using a Vypro® composite mesh: preliminary results about 106 cases. ICS-IUGA 2004 Conference Abstract No. 620, http://www.ics.org/Abstracts/Publish/42/000620.pdf

[15] Benbouzid S, et al. Pelvic organ prolapse transvaginal repair by the Prolift system: evaluation of efficacy and complications after 4.5 years follow up. Int J Urol. 2012;19(11):1010-6; de Landsheere L, et al. Surgical intervention after transvaginal Prolift mesh repair: retrospective single-center study including 524 patients with 3 years' median follow-up. Am J Obstet Gynecol. 2012;206(1):83.e1-7; Feiner B, et al. (2011). A Prospective comparison of two commercial mesh kits in the management of anterior vaginal prolapse. Int Urogynecol J (2012) 23:279-283.

D. PROLIFT PATIENT BROCHURES

Ethicon created patient brochures used to inform patients about Prolift. I will testify that Ethicon's patient brochures appropriately provide basic information to patients and recommend that she discuss her condition and options with her surgeon.

A patient brochure does not replace the patient-surgeon relationship or the related informed consent process. Only a surgeon can determine, using his or her medical judgment, whether a particular patient is a candidate for Prolift.

E. FDA PUBLIC HEALTH NOTIFICATIONS

On October 20, 2008 the FDA issued a Public Health Notification to all healthcare practitioners regarding complications associated with the transvaginal placement of surgical mesh to treat POP and Stress Urinary Incontinence (SUI). It read: "The most frequent complications included erosion through vaginal epithelium, infection, pain, urinary problems, and recurrence of prolapse and/or incontinence. There were also reports of bowel, bladder, and blood vessel perforation during insertion. In some cases, vaginal scarring and mesh erosion led to a significant decrease in patient quality of life due to discomfort and pain, including dyspareunia." [16]

All surgeons implanting Prolift should have sought training on the use of the Gynecare Prolift pelvic floor repair system. Had they done so, they would have learned about the transvaginal entrance into the vesicovaginal space utilizing a full thickness dissection through the vaginal wall thereby minimizing the risk of mesh exposure. They would have learned about

[16] FDA.gov. Transvaginal placement of surgical mesh in repair of pelvic organ prolapse and stress urinary incontinence. 2008

setting the mesh so that it was completely in contact with the tissue without folding or bunching and, most importantly, without tension to minimize the risk of contraction, which surgeons would understand could cause erosion, dyspareunia or vaginal pain.

In the FDA safety communication dated July 13, 2011, FDA recommended that health care providers "obtain specialized training for each mesh placement technique, and be aware of the risks of surgical mesh." Ethicon had been offering professional education since 2005 on the Prolift. In that same communication, FDA warned that the serious complications associated with surgical mesh for transvaginal repair of POP were not rare. Ethicon had been warning of scarring and contraction in their IFU and educational materials since 2005 and the medical literature had also reported scarring and contraction of the tissue as a risk of vaginal and prolapse surgery.[17] This safety communication did not serve as a product recall. Instead, it provided information to surgeons – information that Ethicon had already provided in the Prolift IFU.

F. SUMMARY

The Prolift device has been extensively studied, more so than any other prolapse device. The clinical data and my personal experience show that it is safe and effective.

All interventions carry risk. A complication does not mean that there is a defect. Native tissue prolapse repairs carry significant risks as well. The only unique risk with Prolift is mesh exposure and erosion, which has long been known to be a risk and was warned of in various

[17] FDA.gov. Update on serious complications associated with transvaginal placement of surgical mesh for pelvic organ prolapse: FDA safety communication. 2011

materials such as the IFU, Surgical technique guide, professional education and the Surgeons Resource Monograph.

## II. STRESS URINARY INCONTINENCE

Stress Urinary Incontinence is the involuntary leakage of urine. It is a common problem that impacts women of all ages. Up to 33% of women experience urinary incontinence on a regular basis, although incidence rates vary. There are three types of incontinence: stress urinary incontinence (SUI), urge urinary incontinence (UUI), and mixed incontinence. SUI refers to accidental leakage of urine which occurs with activites like coughing, sneezing, jumping, standing, or lifting heavy objects. UUI refers to sudden urge to urinate followed by leakage of large amounts of urine. Mixed incontinence refers to patients with symptoms of both SUI and UUI.

Some of the known risk factors for stress urinary incontinence include: age, pregnancy/childbirth, obesity, genetic predisposition/ethnic heritage, menopausal status, diabetes, kidney disease, smoking and chronic coughing. Women who suffer from urinary incontinence report reduced quality of life, score low on Quality of Life (QOL) questionnaires, may experience depression, and may experience sexual dysfunction (25-50% of women with SUI experience sexual dysfunction).

There are three treatment options for SUI, including behavior modification, non-surgical treatments, and surgical procedures. Behavioral modifications include weight loss, smoking cessation, control of chronic cough, decreasing fluid intake, and timed voiding. Non-surgical treatments include pelvic muscle (Kegel) exercises, a pessary (a device worn in the vagina that

externally compresses the urethra), and possibly timed voiding. Procedures or surgeries to treat SUI include injection of periurethral bulking agents, mid-urethral mesh slings, cadaveric fascia or autologous fascia pubovaginal slings, or abdominal retropubic urethropexy, including the Marshall-Marchetti-Krantz Procedure (MMK) and the Burch procedure.

A. Treatment of SUI before Mid-Urethral Slings

Before the late 1990s, the most common procedures used to treat SUI were the MMK procedure, the Burch procedure, and the pubovaginal sling procedure.

The MMK Procedure is also known as the retropubic suspension or bladder neck suspension surgery. This procedure is not the procedure of choice today because it involves general anesthesia, requires a 2-3 day hospital stay, can lead to bony or other pelvic complications, and has inferior long-term efficacy.

In the Burch procedure, surgeons attach the paravaginal fascia to Cooper's ligaments. The Burch procedure requires an abdominal incision, is time-consuming, and requires a prolonged rehabilitation. This procedure is not favored by surgeons because of the significant post-operative morbidity, voiding difficulty, de novo pelvic organ prolapse, pain, and delayed failures.

Finally, the pubovaginal sling (PVS) procedure requires the placement of graft material directly under the urethra. The surgeon attaches the graft material to the connective tissue (fascia) of the abdominal muscles. Although the success rate of the sling is good, the long-term success rates may show some decline. In comparison to the Burch, the fascial sling has a higher rate of UTI, urge incontinence, voiding dysfunction, and the need for surgical revision to

improve voiding, such as urethrolysis to relieve urethral obstruction. The increased efficacy but greater morbidity of the fascial sling is echoed in other systematic reviews and in my own practice and experience.

B. Use of Mesh to Treat SUI

The TVT family of products are made from Prolene (polypropylene) mesh. Surgeons have used polypropylene mesh as a permanent human implant for decades. The first meshes were developed and used by hernia surgeons in the 1950s. Ethicon started using Prolene (polypropylene and certain extracts) in sutures in the 1960s. Prolene sutures have been used for various procedures including cardiovascular repairs, plastic surgery, hernia repairs, and pelvic floor repairs. Ethicon used that same material to develop Prolene mesh for hernia surgery in the early 1970s. Based these experiences, the inflammatory response associated with Prolene was widely known long before Prolene was used to treat SUI.

Dr. Ulmsten and Dr. Peter Petros began using mesh to treat stress urinary incontinence, by placing several different types of mesh under the mid-urethra, in the 1990s.[18] The surgeons experimented with several materials including Prolene, Gore-Tex, and Mersilene. Prolene was the most successful. Eventually, Dr. Ulmsten began placing meshes loosely around the urethra, a procedure that became the TVT procedure.

[18] Petros PE, Ulmsten UI (1993), An integral theory and its method for the diagnosis and management of female urinary incontinence. *Scand J Urol Nephrol Suppl*;153: 1-93; Ulmsten U, et al., A multicenter study of tension-free vaginal tape (TVT) for surgical treatment of stress urinary incontinence. *Int Urogynecol J Pelvic Floor Dysfunct* 1998;9(4):210-3; Petros P. (2015) Creating a gold standard surgical device: scientific discoveries leading to TVT and beyond: Ulf Ulmsten Memorial Lecture. *Int Urogynecol J* 26(4):471-76.

Dr. Ulmsten's first trial concluded in 1996 and included 75 patients with a two-year follow-up. [19] 84% (63 patients) of those patients were completely cured and an additional 8% (6 patients) were significantly improved. None of these patients experienced significant intra- or postoperative complications, defective healing, or rejection of the sling.

In 1997, Ethicon began to sell TVT in Europe. In 1998, several surgeons, including Dr. Ulmsten, participated in a prospective randomized study with six centers in Scandinavia to test the safety and efficacy of the TVT device. The study included 131 patients suffering from SUI. 91% (119 patients) of those patients were cured and another 7% (9 patients) were significantly improved.[20]

Since 1998, the literature has substantially supported TVT's safety and efficacy. In fact, more than 80 randomized controlled trials have assessed the TVT and approximately 1,000 studies have addressed the TVT mesh.[21]

C. Gynecare's TVT

Polypropylene mesh slings, such as the TVT, are the most common surgical treatment for SUI. The extensive published studies demonstrate minimal morbidity when compared with alternative surgeries such as Burch, MMK, or PVS. There are several advantages of the sling procedure, including shorter operative time/anesthetic need, reduced surgical pain, reduced

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[19] Ulmsten U, et al. (1996) An ambulatory surgical procedure under local anesthesia for treatment of female urinary incontinence. *Int Urogynecol J* 7:81-86.

[20] Ulmsten U (1998) A multicenter study of tension-free vaginal tape (TVT) for surgical treatment of stress urinary incontinence. *Int Urogynecol J*, 9:210-213.

[21] A systematic review of patient-years of experience in prospective randomized controlled trials (RCTS) in incontinence, ETH.MESH.07246690-719; CER TVT Family of Products, ETH.MESH.10178882- 10179216.

hospitalization, reduced voiding dysfunction, higher long-term success rates, and low complications.[22]

Although mesh-related complications can occur following polypropylene sling placement, the rate of these complications is acceptably low. Furthermore, most sling-related complications such as urinary retention, UTI, and pelvic pain occur with mesh and non-mesh procedures.[23]

1. *TVT Has Been Widely Studied*

There are over 150 Randomized Controlled Trials with TVT and others in its family (TVT-O, TVT-S, etc., as well as those from other companies) establishing their efficacy and safety, including numerous long term studies. These studies demonstrative objective and subjective cure rates for 80-95% of patients.[24]

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[22] American Urological Association, Position Statement on the Use of Vaginal Mesh for the Surgical Treatment of Stress Urinary Incontinence, October 2013.

[23] FDA, Considerations About Surgical Mesh for SUI, April 2, 2013. U.S. Food and Drug Administration http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm345219.htm downloaded Feb 10, 2016; American Urological Association, Position Statement on the Use of Vaginal Mesh for the Surgical Treatment of Stress Urinary Incontinence, October 2013.

[24] Nilsson CG et al. (2008) Eleven years prospective follow-up of the tension-free vaginal tape procedure for treatment of stress urinary incontinence. *Int Urogynecol J* 19:1043-47; Liapis A, et al. (2008) Long-term efficacy of tension-free vaginal tape in the management of stress urinary incontinence in women: efficacy at 5- and 7-year follow-up. *Int Urogynecol J* , 19:1509-12; Olsson I et al. (2010) Long-term efficacy of the tension-free vaginal tape procedure for the treatment of urinary incontinence. *Int Urogynecol J* 21:679-83; Liapis A et al. (2010) Efficacy of inside-out transobturator vaginal tape (TVTO) at 4 years follow up. *Eur J Obstet Gynecol Reprod Biol* 148:199-201; Angioli R, et al. (2010) Tension-free vaginal tape versus transobturator suburethral tape: five-year follow-up results of a prospective, randomised trial. *Eur Urol* 48:671-77; Groutz A, et al. (2011) Ten-year subjective outcome results of the retropubic tension-free vaginal tape for treatment of stress urinary incontinence. *J Minim Invasive Gynecol* 18(6):726-29; Aigmueller T et al. (2011) Ten year follow-up after the tension-free vaginal tape procedure. *Am J Obstet Gynecol* 205:496; Groutz A, et al. (2011) Long-term outcome of transobturator tension-free vaginal tape: efficacy and risk factors for surgical failure. *J Womens Health* 20(10):1525-28; Cheng D, Liu C (2012) Tension-free vaginal tape-obturator in the treatment of stress urinary incontinence: a prospective study with five-year follow-up. *Eur J Obstet Gynecol Reprod Biol* 161(2):228-31; Heinonen P, et al. (2012) Tension-free vaginal tape procedure without preoperative

Dr. Carl Nilsson published 17-year data for the TVT in 2013.[25] Dr. Nilsson reported data for 46 women who were followed postoperatively for 17 years. Of those 46 women, 91.3% (42 women) were objectively cured. These women showed no clinically significant contracture, no tape rejection, and only one mesh exposure, which was asymptomatic and due to vaginal atrophy in an elderly patient who was satisfied with the outcome. This study demonstrated the TVT is safe and effective after 17 years.

The TVT provides a well-known and well-established treatment for SUI and is the most effective procedure for women. The procedure is minimally invasive and safer when compared to alternative procedures, including the Burch procedure and autologous pubovaginal slings. This is further demonstrated in several meta-analyses (Cochrane review), systematic reviews, and guidelines.

Polypropylene mid-urethral slings are the gold standard for treatment of SUI. No other device or SUI surgery has been studied as extensively as TVT. Contrary to Plaintiffs' experts' claims, TVT's long term results clearly demonstrate that complications associated with TVT do not increase over time.

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urodynamic examination: long-term outcome. *Int J Urol* 19(11):1003-09; Serati M et al.(2012) Tension-free vaginal tape for the treatment of urodynamic stress incontinence: efficacy and adverse effects at 10-year follow-up. *Eur Urol* 61:939-46; Nilsson CG et al. (2013), Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. *Int Urogynecol J* 24:1265-69; Svenningsen R (2013) Long-term follow-up of the retropubic tension-free vaginal tape procedure. *Int Urogynecol J* 24:1271-78; Serati M, et al. (2013) TVT-O for the treatment of pure urodynamic stress incontinence: efficacy, adverse effects, and prognostic factors at 5-year follow-up. *Eur Urol* 63:872-78; Laurikainen E et al. (2014) supra; Athanasiou S et al. (2014) Seven years of objective and subjective outcomes of transobturator (TVT-O) vaginal tape: why do tapes fail? *Int Urogynecol J* 25:219-25.

[25] Nilsson CJ et al. (2013), Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. *Int Urogynecol J 19:1043-47*.

2. *TVT is the Safest Procedure*

I am aware that Plaintiffs' experts have opined that procedures including anterior plication, needle suspension, MMK and open and laparoscopic Burch colposuspension are safer alternative procedures when compared to the TVT. Although these procedures are considered native tissue repairs, they do require the use of a permanent suture such as Prolene or Gore-Tex.

It is my opinion that anterior plications, needle suspension (such as the Raz procedure), paravaginal defect repair, and the MMK are not first line treatment options for SUI. The success rates are lower and the risks are more serious than MUS.[26]

D. Alleged Complications Associated with TVT

Plaintiffs' experts claim that TVT is associated with several complications, including infection, inflammation, cytotoxicity, contraction, degradation, and cancer. Those claims are supported by neither evidence-based studies nor my personal experience.

1. *Infection Rates are Low*

Contrary to Plaintiffs' experts' contention, infection rates are very low. Also, Ethicon, through the TVT IFU, warns of the possibility of infection when implanting a TVT device. The IFU also warns that removal maybe necessary in some cases of persistent infection. Infections are

[26] National Institute for Health and Care Excellence, Urinary incontinence: The management of urinary incontinence in women, Sept. 2013 at guidance.nice.org.uk/cg171; American Urological Association, Position Statement on the Use of Vaginal Mesh for the Surgical Treatment of Stress Urinary Incontinence, October 2013; American College of Obstetricians and Gynecology, Practice Bulletin Summary, 126 (5), November 2015.

no more common with TVT mesh than they are with native tissue repairs. Furthermore, any infection can usually be treated without removal of the mesh.[27]

2. *Inflammation is not Clinically Significant*

Plaintiffs' experts have suggested that there may be an inappropriate inflammatory response associated with the TVT. In my practice, I have not experienced a significant inflammatory response with TVT. Nor is it demonstrated in the literature from peer-reviewed urology, urogynecology, or gynecology journals. It is known and accepted that there will be some level of inflammatory response with any foreign body. In my experience, this degree of inflammation is not clinically harmful or significant in that it rarely causes chronic pain, infection or adversely affects adjoining structures.

3. *TVT is not Cytotoxic*

Any claim that TVT is cytotoxic in women is not credible. The long-term studies and data do not show cytotoxicity, and their results are contrary to Plaintiffs' experts' theories.

4. *TVT Mesh Does Not Curl or Significantly Contract*

Contrary to Plaintiff's experts' contention, TVT mesh does not curl, significantly contract, or experience pore collapse when implanted as directed in the IFU. This is supported by the literature and my personal experience. If contraction occurs at some unseen level, it is not clinically significant.

[27] Amin P, et al. (1994) Biomaterials and Abdominal Wall Hernia Surgery, Inguinal Hernia: Advances or Controversies, Radcliffe Medical Press; Amin P, et al. (1997) Classification of biomaterials and their related complications in abdominal wall hernia surgery, Hernia (1997) 1: 15-21; FDA Polypropylene Reclassification Letter, July 5, 1990.

Scar tissue contracts in any pelvic surgery. If the TVT mesh had significant contracture, it would contract uniformly, chronically elevating the bladder and leaving almost all patients with voiding dysfunction. Clinically significant tissue contraction is a rare complication.

5. *TVT Mesh Does Not Degrade*

Clinical evidence, including my own clinical experience, establishes that TVT mesh does not degrade. If it does, any such degradation does not lead to a clinically significant effect. Instead, long-term clinical studies show lasting success and low to no late-term complications with TVT.

6. *TVT Mesh Does Not Cause Cancer*

Finally, there is no reliable scientific information to support Plaintiffs' experts' claim that polypropylene can cause cancer or sarcoma. Medical literature is devoid of reports of tumors related to the implantation of surgical-grade polypropylene for midurethral slings. In fact, recent published studies from the Mayo and Cleveland Clinics show no association between polypropylene MUS and cancer.[28]

E. Official Guidelines from Governmental Agencies or Medical Societies Regarding SUI surgery and Slings

Several governmental agencies and medical societies have published guidelines addressing SUI surgery and slings. These agencies include the American Urogynecologic Society

[28] Moore C, et al (2014), Is There an Association Between Polypropylene Midurethral Slings and Malignancy? *Female Urology* 84 (4), 2014; Moalli P, et al (2014), Polypropylene mesh: evidence for lack of carcinogenicity. *Int Urogynecol J* DOI 10.1007/s00192-014-2343-8; King AB, et al. (2014) Current controversies regarding oncologic risk associated with polypropylene midurethral slings. *Curr Urol Rep* 15:453; Sunoco MSDS; AUGS & SUFU, Frequently Asked Questions by Providers—Mid-urethral Slings for Stress Urinary Incontinence. (available at http://www.augs.org/p/bl/et/blogaid=194); King AB et al. (2014), Is there an association between polypropylene MVS and malignancy? *Urology* 84:789-792; Linder B, et al (2016), Evaluation of the local carcinogenic potential of mesh used in the treatment of female stress urinary incontinence. *Int Urogynecol J* DOI 10.1007/s00192-016-2961-4.

("AUGS")[29], the Society of Urodynamics and Female Urology ("SUFU"), the International Continence Society ("ICS"), the American Urological Association ("AUA"), the Food and Drug Administration ("FDA"), and the National Institute for Health and Care Excellence ("NICE"). Each of these entities has published various statements advocating the use of synthetic mid-urethral slings in the treatment of Stress Urinary Incontinence in women. Each of these statements are well-reasoned and consistent with the medical literature and my clinical experience. Accordingly, I agree with each of these statements.

As an example, FDA published a statement 2013. There, the FDA concluded that "[t]he safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to one-year." In 2014 AUGS published a short and clear statement about the proven efficacy and safety of MUS. AUA published its own in November 2011 and October 2013[30], and the publication of others continues to this day.

F. The TVT Warnings are Sufficient

1. *Patient Brochure*

I have reviewed the patient brochures for TVT. I will testify that the patient brochures adequately convey basic information to the lay person and recommend that the patient discuss her condition and options with her surgeon.

[29] American Urogynecologic Society and Society of Urodynamics and Female Urology joint position statement on midurethral slings; American Urogynecologic Society Position Statement on Restrictions of Surgical Options for Pelvic Floor Disorders, March 2013.

[30] American Urological Association, Position Statement on the Use of Vaginal Mesh for the Surgical Treatment of Stress Urinary Incontinence, November 2011; American Urological Association, Update to the Position Statement on the Use of Vaginal Mesh for the Surgical Treatment of Stress Urinary Incontinence, October 2013.

Importantly, a patient brochure is not intended to replace the patient-surgeon relationship and informed consent process. Only a trained surgeon knows whether TVT is appropriate based upon the particular patient's background, history, and presentation.

2. *Instructions for Use*

I am familiar with Instructions For Use (IFU) generally from my experience in the use of medical devices. I have reviewed the IFU for TVT. It fairly and adequately informs reasonably prudent surgeons of the indications for TVT, the associated procedure, and the potential risks and complications.

Importantly, an IFU is not intended to be a comprehensive training guide for the surgical treatment of SUI. Instead, surgeons operating within the standard of care should already be familiar with the risks, potential complications, and benefits associated with pelvic surgery, with or without mesh. The FDA has acknowledged that risks known to be common to pelvic floor surgery (even without mesh) include pain, infection, urinary problems, recurrent incontinence, pain during sexual intercourse (dyspareunia), bleeding, organ perforation, neuro-muscular problems and vaginal scarring.[31]

[31] FDA, Considerations About Surgical Mesh for SUI, April 2, 2013. U.S. Food and Drug Administration http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm345219.htm downloaded Feb 10, 2016.